REMARKS

Applicants thank the Examiner for her review of Applicants previous response. Applicants acknowledge the Examiners acceptance of the change of inventorship; the withdrawal of the rejection of Claims 4-6 under 35 U.S.C. § 101 for lack of utility; the withdrawal of the rejection of Claims 4 and 5 under 35 U.S.C. § 112, first paragraph, written description; and the withdrawal of the rejection of Claims 1-6, 8-10, and 14-16 under 35 U.S.C. § 102(b) as anticipated by GenBank Accession No. AF184971.

Applicants note that the Examiner has neither maintained nor withdrawn the rejection of Claims 1-6 and 17-20 under 35 U.S.C. § 103(a) as being unpatentable over GenBank Database Accession No. AF184971. Applicants request that the Examiner confirm for the record that this rejection was withdrawn as well.

Applicants have canceled Claims 14, 16 and 21-25 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application. Applicants have amended Claims 4, 5, 26 and 27 to recite the additional limitation "wherein said nucleic acid sequence identity between the isolated nucleic acid and the sequence of interest is determined without introducing a gap into either of the nucleotide sequences being compared, so as to increase the number of aligned nucleotides." Applicants submit that no new matter has been added by the amendments, and that support for the amendments can be found throughout the specification, for example, at ¶¶ [0211]-[0219] of the specification. Applicants have added new Claim 32. Support for this claims is found, for example, in ¶¶ [0009] and [0010] of the specification.

Claims 4-6, 11-13, 17-20, and 26-32 are presented for examination. For the reasons stated below, Applicants respectfully traverse the rejections of the pending claims.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 14-31 under 35 U.S.C. § 101 as lacking a specific, substantial, and credible utility. The PTO argues that utilities asserted in the specification are not specific and substantial or well established. The PTO has accepted the utility of Claims 4-6, and presumably dependent Claims 11-13, as diagnostic tools for cancer based on the data in Example 18 which discloses that SEQ ID NO:75 is more highly expressed in esophageal tumors compared

to normal esophageal tissue. Office Action at 2. However, the PTO states that "[i]f the claimed polynucleotide is not more highly expressed in esophageal tumor, one cannot use it." Office Action at 4. The PTO also states that "it was not routine to use as tumor probe a nucleic acid less than 100% identical to the target nucleic acid. There are no working examples of nucleic acids at least 95% identical to or hybridizing under the recited conditions which are overexpressed in esophageal tumors other than SEQ ID NO: 75 itself." Office Action at 5. The PTO also argues throughout that Claims 14, 16 and 19-31 do not have any functional limitations.

The PTO quotes Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for the assertion that: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful." Office Action at 7. The PTO concludes that "it is not clear that the expression changes listed in Example 18 of the instant specification are significant." *Id.*

Applicants respectfully disagree and submit that for the reasons stated below, all of the claimed nucleic acids have a credible, substantial, and specific utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any*

reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to

> convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify their argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed nucleic acids have utility as diagnostic tools for cancer, particularly esophageal cancer. Applicants' asserted utility rests on the following argument:

1. Applicants assert they have provided reliable evidence that mRNA for the PRO1315 polypeptide is expressed at least two-fold higher in esophageal tumor compared to normal esophageal tissue, and therefore the claimed nucleic acids are useful as diagnostic tools. Applicants are not asserting that the claimed nucleic acids will necessarily provide a definitive

diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. The PTO has accepted this asserted utility with respect to Claims 4-6, and presumably dependent Claims 11-13;

2. A nucleic acid which hybridizes to the disclosed nucleic acids that are differentially expressed in esophageal tumors is useful as a diagnostic tool for cancer, regardless of whether it is less than 100% identical to the target sequence.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has alleged that unless the nucleic acid is overexpressed in esophageal tumors, it is not useful;

2. The PTO argues that it was not routine to use as tumor probe a nucleic acid less than 100% identical to the target nucleic acid;

3 The PTO cites Hu for the assertion that it is not known if the results of Example 18 are biologically meaningful.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, a probe for a nucleic acid which is differentially expressed in cancer is certainly useful, even if the probe sequence itself is not differentially expressed and even it is not identical to the target sequence; second, the PTO has accepted that the results of Example 18 are sufficient to establish utility for the nucleic acids of Claims 4-6, and therefore Hu is not relevant to the utility rejection of Claims 14-31.

Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. **The standard is not absolute or statistical certainty**.

Applicants have established that the Gene Encoding the PRO1315 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants have asserted, and the PTO has accepted, that the nucleic acid of SEQ ID NO:75 is more highly expressed in esophageal tumor than normal esophageal tissue, and therefore the nucleic acid has utility as a tumor marker for esophageal tumors. Office Action at 3. Because this utility has been established, any questions regarding the sufficiency of the disclosure in Example 18 and the rest of the application to establish a utility for SEQ ID NO:75 are now moot.

The PTO has alleged that unless the nucleic acid is overexpressed in esophageal tumors, it is not useful. Applicants note that the PTO has not provided any reasoning or supporting evidence for this assertion. To the contrary, Applicants assert that one of skill in the art would recognize that to detect the differential expression of SEQ ID NO:75 in esophageal tumors, one could use a nucleic acid which hybridizes to SEQ ID NO:75 under stringent conditions as a probe for SEQ ID NO: 75. This use is contemplated and disclosed in the instant application at, for example, ¶¶ [0012], [0025], [0220], [0225]-[00228], [0311], and [0317]. Such probes of SEQ ID NO:75 do not also need to be overexpressed in esophageal tumors to be useful.

Regarding the PTO's assertion that "it was not routine to use as a tumor probe a nucleic acid less than 100% identical to the target nucleic acid" (Office Action at 5), this assertion represents official notice without documentary evidence. Since the routine percent identity of a probe to its target is not common knowledge or well-known, Applicants request documentary evidence in support of the noticed fact, in accordance with *In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001).

And even assuming that the PTO can establish that it was not routine to use probes with less than 100% identity to the target nucleic acid, this does not in any way establish that the claimed nucleic acids of Claims 26 and 27 which hybridize to the disclosed sequences under the recited high stringency conditions cannot be used as probes, even if it was not routine to do so. Applicants remind the PTO that the asserted utility does not need to be the best way to achieve the desired result, nor does it need to be better than existing methods. The Court of Appeals for the Federal Circuit has stated that the standard for satisfying the utility requirement is a low one:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. *See Brenner v. Manson,* 383 U.S. 519, 534, 86 S.Ct. 1033, 16 L.Ed.2d 69 (1966); *Brooktree Corp. v. Advanced*

> *Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger,* 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end"). *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q. 2d 1700 (Fed. Cir. 1999) (emphasis added).

The low threshold for satisfying the utility requirement is reflected in the standard set by the Federal Circuit for invalidating a patent based on a lack of utility: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility. Some degree of utility is sufficient for patentability. Further, the defense of non-utility cannot be sustained without proof of total incapacity." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 U.S.P.Q. 473 (Fed. Cir. 1984) (emphasis added, citations omitted).

Finally, the PTO quotes Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for the assertion that: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful." Office Action at 7. The PTO concludes that "it is not clear that the expression changes listed in Example 18 of the instant specification are significant." *Id.*

Because the PTO chooses to combine the discussion of the enablement and utility rejections, Applicants are not clear if the PTO is asserting that the results of Example 18 are insufficient to establish a utility. This does not appear to be the case, as the PTO has already stated that "the asserted utility for the nucleic acid as a tumor marker for esophageal tumor is accepted." Office Action at 3 (emphasis in original). Therefore, Applicants must assume that the discussion of Hu is in relation to the PTO's enablement rejection, not the utility rejection.

However, if the PTO is asserting that Hu somehow supports the utility rejection of the pending claims, Applicants have already established that it is not necessary to know the role of PRO1315 in cancer to use it as a biological marker. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute Applicants' assertion that the PRO1315 gene can be used as a cancer diagnostic tool because it is

differentially expressed in certain tumors. Similarly, Hu does not refute Applicants' assertion that nucleic acids which hybridize to SEQ ID NO:75 under the recited stringent conditions can also be used as probes for detecting the differential expression of PRO1315 in esophageal tumors.

As the Applicants previously pointed out, the position of the PTO is inconsistent with the analogous standard for therapeutic utility of a compound that "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public. The same is true of the rejected subject matter which can be used to detect this differential expression.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Hu is not sufficient to prove that a person of skill in the art would consider it unlikely that nucleic acids which can be used to detect a gene differentially expressed in certain tumors are useful as diagnostic tools, since Hu does not address this issue. Given the lack of support for the PTO's position, and the supporting evidence provided by the Applicants, one of skill in the art would be more likely than not to believe that the claimed nucleic acids which hybridize to the nucleic acids related to SEQ ID NO:75 can be used as diagnostic tools for cancer, particularly esophageal cancer.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that nucleic acids which have at least 95% sequence identity to, and hybridize to, a nucleic acid that is differentially expressed in certain tumors can be used as a diagnostic tool. Given the lack of support for the PTO's position and the fact that the PTO has accepted the asserted utility for Claims 4-6, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement for the rejected claims. And even if the PTO has met that burden, the Applicants' supporting rebuttal arguments are sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed nucleic acids can be used as diagnostic tools for cancer, particularly esophageal cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Applicants next address the PTO's rejection of the claims based on a lack of a specific utility.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1315 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the gene encoding the PRO1315 polypeptide is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue. These data are strong evidence that the gene encoding the PRO1315 polypeptide is associated with esophageal tumors. Thus, Applicants submit that they have provided evidence associating the gene encoding PRO1315 with a specific disease. As mentioned above, the PTO has already accepted this asserted utility for Claims 4-6.

The pending claims which remain rejected under 35 U.S.C. § 101 for lack of utility have very high sequence homology to the disclosed sequences (*e.g.*, SEQ ID NO:75), and can be used as probes to detect the differential expression of SEQ ID NO:75 in esophageal tumors. This asserted utility as a diagnostic tool for cancer, particularly esophageal tumor, is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted three arguments for why there is a lack of a substantial utility: (1) the PTO has alleged that unless the nucleic acid is overexpressed in esophageal tumors, it is not useful; (2) the PTO argues that it was not routine to use as tumor probe a nucleic acid less than 100% identical to the target nucleic acid; and (3) the PTO cites Hu for the assertion that it is not known if the results of Example 18 are biologically meaningful. Applicants have addressed each of these arguments in turn.

First, the Applicants have argued that contrary to the PTO's unsupported arguments, the claimed nucleic acids do not have to be overexpressed in esophageal tumors to be useful since they can be used as probes for the recited sequences related to SEQ ID NO:75. Second, even if

the PTO can establish its unsupported assertion that it is not routine in the art to use probes with less than 100% sequence identity to the target sequence, the PTO has not explained how this supports a rejection of the claimed nucleic acids as lacking utility. Whether it is routine or not, one of skill in the art would readily recognize, and Applicants have disclosed, that sequences with less than 100% identity can be used as probes. Third, Applicants have shown that Hu is in no way contrary to the asserted utility for the rejected claims. Whether PRO1315 has a role in cancer is irrelevant to the use of the claimed nucleic acids as diagnostic tools for cancer.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the gene encoding PRO1315 is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of nucleic acids.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids relating to PRO1315 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO rejected pending Claims 4-6, 11-13, 17-20 and 26-31 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that undue experimentation would be required to make and/or use the claimed nucleic acids.

Applicants respectfully traverse.

Applicants submit that one skilled in the art could have made and used the claimed nucleic acids without undue experimentation. The PTO evaluates the invention in the light of factors to be considered for enablement (herein referred to as "Wands factors") in asserting that the claimed nucleic acids cannot be used without undue experimentation.

Applicants first address whether one skilled in the art could have used the claimed nucleic acids without undue experimentation.

The PTO considers several Wands factors in concluding that the claimed nucleic acids lack enablement. Regarding the nature of the invention, the state of the prior art, and the skill in the art, the PTO acknowledges that nucleic acids could be used as tumor markers and screening methods were known, but the PTO asserts that nucleic acids similar to SEQ ID NO:75 had been identified in the art but this art does not help elucidate a enabling use for the claimed subject matter, that interpretation of differential screening methods depended on differences in levels, the ability to generalize and reproduce results, and the ability to pinpoint tumor type. The PTO also asserts that it was not routine in the art to use as a tumor probe a nucleic acid less than 100% identical to the target nucleic acid. Regarding the specification, the PTO states that there are no working examples and little guidance provided for using the claimed nucleic acids. The PTO states that the specification fails to disclose the specific type of tumor, level of expression, relative amounts, and how many different cDNA libraries were screened. Regarding the breadth of the claims, the PTO concludes that the claims are broad. Based on these considerations, the PTO determines that it would have required undue experimentation to use the claimed nucleic acids.

Applicants respectfully submit that, one skilled in the art, in view of the teachings of the specification, could have readily used the claimed nucleic acids.

Regarding the state of and level of skill in the art, Applicants submit that one skilled in the art knew how to use nucleic acids, such as the claimed nucleic acids, as diagnostic tools for

cancer, particularly esophageal cancer. The PTO has acknowledged this utility for Claims 4-6 and presumably Claims 11-13, and for the reasons detailed above, the remaining claims are also useful, for example as hybridization probes for SEQ ID NO:75. As acknowledged by the PTO, nucleic acid methods such as differential screening methods have been routine for more than a decade. Further, it is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, it unquestionable that one skilled in the art knew how to use a nucleic acid such as the recited nucleic acids in nucleic acid methods such as hybridization assays of samples. *See also Specification* at, for example ¶¶ [0012], [0025], [0220], [0225]-[00228], [0311], and [0317] (disclosing the use of the claimed nucleic acids as hybridization probes using well established methods).

Regarding the PTO's assertion that "it was not routine to use as a tumor probe a nucleic acid less than 100% identical to the target nucleic acid" (Office Action at 4), this assertion represents official notice without documentary evidence. Since the routine percent identity of a probe to its target is not common knowledge or well-known, Applicants request documentary evidence in support of the noticed fact, in accordance with *In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001).

And even assuming that the PTO can establish that it was not routine to use probes with less than 100% identity to the target nucleic acid, this does not in any way establish that the it would require undue experimentation, even if it was not routine to do so. Applicants assert that the PTO must establish that changing the sequence identity from 100% to 95% or 99% would somehow require undue experimentation. An unsupported statement that it was not "routine" to do so in no way establishes that varying from what was "routine" requires undue experimentation.

Regarding the teachings of the specification, Applicants submit that specific guidance and a working example are provided in Applicants' disclosure. The specification, for example, at paragraphs [0311] and [0449]-[0452] (Example 5), teaches various methods for using the claimed nucleic acids, for example, in hybridization assays of samples. The specification also provides a working example, Example 18 (paragraph [0530]), in which differential expression experiments are described, and the results of the experiments revealed that in esophageal tissue, the nucleic acid encoding PRO1315 was more highly expressed in tumor relative to normal.

Furthermore, the PTO has recognized the fact that the claimed nucleic acids are useful as tumor markers, stating "the asserted utility for the nucleic acid as a tumor marker for esophageal tumor is accepted," (Office Action at 3) and Applicants have demonstrated that the remaining claimed subject matter is also useful as diagnostic tools for cancer. Accordingly, the PTO recognizes that the claimed nucleic acids are useful as tumor markers, and the specification provides specific teachings and a working example of methods and specific organs to target in tumor detection methods.

In sum, nucleic acid methods such as hybridization methods are routine, as acknowledged by the PTO. The claimed nucleic acids have utility as tumor markers, as acknowledged by the PTO. The specification provides guidance on methods for using the claimed nucleic acids. The specification also provides a working example identifying particular organs to target in using the claimed nucleic acids. Since it was routine in the art to use nucleic acids in, for example, hybridization methods of nucleic acid detection, one skilled in the art would need no more than routine experimentation to use the claimed nucleic acids to detect PRO1315 nucleic acids in esophageal samples.

The PTO indicates that the specification is insufficient because the specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. M.P.E.P. §2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Based on the teachings of the specification and the level of skill in the art, it was routine to use nucleic acids such as the claimed nucleic acids in hybridization assays, differential expression in tumor versus normal tissue was established, and one skilled in the art knew which particular organs to target for detection with the nucleic acids. No undue experimentation was required for a Ph.D. scientist with several years of experience to use these routine methods, in view of the teachings in the specification, in order to determine details such as the exact location of the PRO1315 nucleic acid or to determine specific details of differential

expression between normal and tumor. Accordingly, it would not have required undue experimentation for one skilled in the art to make and use the claimed nucleic acids. The claimed invention is, therefore, fully enabled.

The PTO dismisses the Declaration by Grimaldi because it allegedly does not fill important gaps in the disclosure such as "expression level range for normal and tumor tissues, specific types of esophageal tumors detectable, and probability of detection for any particular esophageal tumor type." As discussed above, nucleic acid methods were routine in the art, and the need to test more than one sample in refining specific details of experimental parameters does not represent undue experimentation. The Grimaldi Declaration describes the assays conducted and explains the results of Example 18 were indicative of at least a two-fold difference in expression between tumor and normal samples. This Declaration further underscores that it would have been no more than routine experimentation to use the claimed nucleic acids in methods such as, for example, the method of Example 18.

The PTO cites the publication by Hu et al. for the proposition that it is unclear if the expression changes in Example 18 are significant. The PTO quotes the portion of Hu stating:

> It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful.

As the PTO has asserted, Hu studied differential gene expression and a *known* role in a disease. Office Action mailed February 8, 2005, at 3. Thus, Hu's analysis of differential expression of a gene whose role in a disease is "biologically meaningful" to the disease is completely different from Applicants' asserted differential expression of a gene for diagnostic purposes. Even if a gene does not have a meaningful role in causing a disease, this does not indicate that the gene does not show a consistent and measurable change in expression in the cancer. Whether or not a differentially expressed gene has a biologically meaningful role in a disease does not change the fact that differential expression of a gene and encoded polypeptide can be used in diagnosis of a disease. The lack of a biologically meaningful role of PRO1315 in cancer, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1315 is differentially expressed, or the biological meaning of the differential expression, in order to exploit the differential expression to distinguish tumor from normal tissue.

Further, as noted above, the utility of the PRO1315 nucleic acid is accepted by the PTO. Thus, insofar as the PTO is using Hu to challenge the utility of the claimed nucleic acids by questioning the validity of Applicants data regarding differential expression of the nucleic acid encoding the PRO1315 polypeptide, this point is now moot.

Applicants turn next to the question of whether it would require undue experimentation to make the claimed nucleic acids. As amended, the pending claims are directed to nucleic acids that have at least 95% or 99% nucleic acid sequence identity to the recited sequences and are "more highly expressed in esophageal tumor tissue compared to normal esophageal tissue," nucleic acids identical to SEQ ID NO:75 and related sequences, and finally, nucleic acids that have at least 95% or 99% nucleic acid sequence identity to the recited sequences and which "hybridizes to the complement of a nucleic acid of SEQ ID NO: 75" under the recited stringent conditions.

Applicants submit that one of skill in the art would know how to make the claimed nucleic acids. First, the PTO has apparently accepted that one of skill in the art would know how to make the nucleic acids which are identical to SEQ ID NO:75 and related sequences, as the PTO has not offered any arguments to the contrary.

Second, Applicants submit that it is well-established in the art how to make the nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences related to SEQ ID NO: 75. The PTO has not offered any reason or evidence which disputes this assertion.

With respect to the nucleic acids which have at least 95% or 99% nucleic acid sequence identity to the recited sequences and are "more highly expressed in esophageal tumor tissue compared to normal esophageal tissue," the PTO state that the specification has not provided any guidance "about predicting what other structurally related nucleic acids would have the necessary expression [of overexpression in esophageal tumors]." Office Action at 8.

Contrary to the PTO's assertion, Applicants have disclosed how to find related naturally occurring sequences to SEQ ID NO:75 using hybridization probes to screen cancer and normal tissue libraries. This procedure is described in detail in the specification, for example, in Example 5, ¶¶ [0448]-[0452]. In addition, Applicants have disclosed how to determine if the recited nucleic acids are differentially expressed in esophageal tumors compared to their normal counterparts (*see, e.g.,* Example 18 beginning at paragraph [0529] of the specification).

With respect to the nucleic acids which have at least 95% or 99% nucleic acid sequence identity to the recited sequences and which "hybridizes to the complement of a nucleic acid of SEQ ID NO: 75" under the recited stringent conditions, the PTO argues that "it would require undue experimentation to make a nucleic acid which is both 95-99% identical to or which hybridizes to SEQ ID NO:75 and which is more highly expressed in esophageal tumors compared to normal esophageal tissue, respectively." Office Action at 8 (emphasis in original.)

Applicants first note that Claims 26-31 do not require both hybridization to SEQ ID NO:75 and overexpression in esophageal tumors. Instead, these claims require only that the nucleic acids have at least 95% or 99% sequence identity to the recited sequences, and that they hybridize to the complement of SEQ ID NO:75 under the recited high stringency conditions. As discussed above, it is well within the skill of those in the art to make nucleic acids which are at least 95% or 99% identical to the recited sequences. In addition, it is well-known in the art how to determine if the claimed nucleic acids hybridize to the disclosed sequences under the specified stringent conditions. The PTO has not offered any evidence or arguments to the contrary. Thus, one of skill in the art would know how to make the claimed nucleic acids.

In view of the teachings in the specification and the knowledge in the art, Applicants submit that the claimed nucleic acids are fully enabled, as one of skill in the art would know how to make and use the claimed subject matter without undue experimentation. This assertion is supported by the teachings in the specification, the acknowledged utility of SEQ ID NO:75 as a marker of esophageal tumors, Applicants arguments establishing utility for the remaining claimed nucleic acids as diagnostic tools, as well as the second Grimaldi Declaration. Further, the reference by Hu provides no basis to question the ability of one skilled in the art to use of the claimed nucleic acids. Accordingly, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO rejects pending Claims 17-20 and 26-31 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. The PTO states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of

the invention. The PTO argues that the instant case is not distinguishable from *Fiddes v. Baird* and is not similar to *Enzo Biochem v. Gen-Probe Inc.* because the instant claims, unlike those in *Enzo*, have no functional limitation. Applicants respectfully disagree.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As an initial matter, Applicants note that the PTO has withdrawn the written description rejection of Claim 4, from which rejected Claims 17-20 depend. Applicants assume that the rejection of Claims 17-20 are therefore in error, as the PTO has not made any arguments regarding a lack of written description of these dependent claims.

The subject matter of the remaining rejected pending claims concerns nucleic acids having at least 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO:75, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:75, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203247, with the functional recitation "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO:75" under the specified conditions, as well dependent claims thereto. Applicants note that the specification teaches that percent sequence identity is calculated by dividing the total number of identically matched nucleotides between the two sequences being compared by the total number of nucleotides in the reference sequence. That means that a small nucleic acid (*e.g.*, one which is half or two-thirds the length of the reference sequence), will not meet the 95% or 99% sequence identity limitations even if it is identical to reference sequence. For example, if the reference sequence is 1000 nucleotides, a nucleic acid that is only 600 nucleotides can have at best 60% sequence identity.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original).

In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules. The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. This is contrary to the PTO's argument the claimed sequences do not possess any particular conserved structure, or other disclosed distinguishing feature. The common element or attribute of the claimed genus is that species of the genus are structurally related to SEQ ID NO:75, such that they hybridize to SEQ ID NO:75 or the related sequences under the specified high stringency conditions recited in the claims.

The present situation is not analogous to *Fiddes v. Baird*, 30 U.S.P.Q.2d 1481, cited by the PTO. Unlike *Fiddes*, where arguably the structure of other mammalian sequences could not be conceived based on a single species of the genus, here the skill in the art is such that the sequence of nucleic acids which hybridize to SEQ ID NO:75 under the conditions specified can be conceived. Here, the claimed genus is defined by its structure – members of the genus hybridize under the specified conditions to the specified sequences, each of which are adequately described in the specification.

Applicants note that pending Claims 26-31 are analogous to the claims discussed in Example 9 and Example 14 of the written description training materials. In Example 9, the

written description requirement was found to be satisfied with respect to claims reciting polynucleotides which hybridize to particular nucleic acids under stringent conditions even though the specification did not contain a working example clearly demonstrating the existence of homologous nucleic acids. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity even though the applicant had not made any variants.

The PTO has responded to these arguments by stating that the instant case is similar to *Fiddes* "because the structure of other nucleic acids with the same expression pattern and the required structural limitations cannot be conceived based on the single species disclosed." Office Action at 9-10 (emphasis in original). Applicants submit that this argument is misplaced, as the pending rejected claims do not require the same expression pattern. Rather, they require a similar structure (at least 95% sequence identity) and the function of hybridization to the SEQ ID NO:75 under the recited sequences. Therefore, the PTO's argument regarding conception of a nucleic acid with the same expression pattern is not relevant to the rejected claims.

The PTO also argues that in *Enzo*, the claims required comparative hybridization that demonstrates specificity of the claimed composition for one strain of *Neisseria* over another, and unlike the claims in *Enzo*, "the instant claims have *no* functional limitations." Office Action at 10. The PTO also states that unlike Example 9 of the Written Description guidelines, "nucleic acids claimed herein are not required to encode a protein, much less one with adenylate cyclase or other well-characterized activity." Office Action at 10.

Applicants respectfully submit that the PTO has missed the point of Applicants' reliance on *Enzo*. First, the comparative hybridization limitation does not distinguish *Enzo* from the instant claims, since the comparative hybridization limitation was simply a means of demonstrating the specificity of the claimed composition for one sequence over another. Similarly, the instant claims have recited specific high stringency conditions which likewise establish the requisite amount of specificity the claimed nucleic acids must possess.

Secondly, the Court in *Enzo* clearly indicated that hybridization to a particular sequence, comparative or otherwise, *is* a functional limitation. The Court clearly viewed hybridization to a disclosed structure (*e.g.* SEQ ID NO:75) as a valid structure-function relationship which may adequately describe a nucleic acid. *See Enzo*, 323 F.3d at 968 (stating that on remand the court

must determine if Enzo's disclosure of "the hybridization function and an accessible structure" adequately describes the claimed subject matter) (emphasis added). Therefore, contrary to the PTO's assertion, the instant claims do have a functional limitation – hybridization to SEQ ID NO:75 and the other recited sequences. It is the burden of the PTO to establish that one of skill in the art would not recognize the distinguishing features of the claimed nucleic acids given the disclosure of the structure of SEQ ID NO:75 and the function of hybridization to SEQ ID NO:75 under the specified stringent conditions.

Similarly, Example 9 of the Written Description Guidelines clearly shows that reduction to practice of a single species (*e.g.*, SEQ ID NO:75) is sufficient to describe a genus of nucleic acids which hybridize to the disclosed sequence under stringent conditions. While Example 9 has the additional information that the hybridized sequences encode a protein with adenylate cyclase activity, the PTO has not explained how one of skill in the art would require this additional information to find the claimed nucleic acids adequately described. In fact, it is more difficult for one of skill in the art to know which nucleic acids have both the hybridization *and* adenylate cyclase encoding characteristics than it is to know which nucleic acids only hybridize to the disclosed sequence. Arguably, the additional limitation of encoding an adenylate cyclase makes the written description less adequate, rather than more adequate. Applicants contend that it is enough to recite the conditions under which the claimed nucleic acids hybridize to the disclosed sequences.

In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
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> ***

> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

Given the degenerate nature of the genetic code, a large polypeptide is encoded by a vast number of different nucleic acid sequences. Yet the Court did not require the Applicants in *Wallach* to actually make and individually describe all of the sequences which encode the disclosed polypeptide sequence. This is in spite of the fact that there is no possibility that even the most skilled artisan could envision the detailed chemical structure of all or a significant number of encompassed polynucleotides. Because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to describe the very large genus of nucleic acids which could encode the polypeptide sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:75, and claim nucleic acids which are homologous to it and have the functional limitation of hybridizing to the disclosed sequence under the specified stringent conditions. It is routine in the art to create nucleic acids which have at least 95% or 99% sequence identity to SEQ ID NO:75 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the skill of those in the art to determine which nucleic acids will hybridize to the disclosed sequence under the specified conditions. This structure/function combination of a disclosed sequence and specified stringent condition is sufficient to describe the claimed nucleic acids. The *Wallach* opinion makes clear that there is no need to list each individual sequence within the genus, or be able to visualize their detailed chemical structure, to adequately describe the genus.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:75, by requiring a high degree of structural similarity, and by specifying the high stringency conditions under which hybridization occurs, all of which result in a lack of substantial variability in the species falling within the scope of the rejected pending claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the

members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. § 112, second paragraph

The PTO rejected Claims 14, 16, 21-25 and dependent Claims 17-20 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO states that it is unclear what range is intended by the phrase "at least about."

Applicants have canceled Claims 14, 16, and 21-25 and therefore this rejection is moot. Applicants note that dependent Claims 17-20 do not recited the objected to limitation. Therefore Applicants request that the Examiner withdraw the indefiniteness rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. §102(e) – Anticipation

The PTO rejects Claims 4 and 12-17 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,945,511. The PTO argues that the '511 patent discloses polynucleotide SEQ ID NO: 1 which is at least 99% identical to the region encoding the extracellular domain of SEQ ID NO:76, and SEQ ID NO:76 minus its signal sequence. The PTO also argues that SEQ ID NO: 1 is at least 95% identical to the full-length coding region of SEQ ID NO: 75.

Applicants have previously amended the claims to delete any reference to the encoded polypeptide, therefore, whether SEQ ID NO:1 of the cited reference is 99% identical to the region of SEQ ID NO: 75 encoding the extracellular domain of SEQ ID NO:76 is irrelevant. As to the PTO's argument that "SEQ ID NO: 1 is at least 95% identical to the full-length coding region of SEQ ID NO: 75," Applicants respectfully disagree.

The PTO relies on the sequence alignment in the previous Office Action, which is between Accession No. AF184971 and SEQ ID NO:75. The PTO has not established that this is the same sequence disclosed in U.S. Patent No. 5,945,511. Even assuming that they are the same sequence, the full-length coding region of SEQ ID NO:75 is from nucleotides 121 to nucleotide 1449, a total of 1329 nucleotides. The alignment in the previous Office Action shows an alignment of the two sequences from nucleotide 189 to nucleotide 1449 of the full-length coding sequences, with two mismatches, for a total of 1259 identical nucleotides. This means that the

cited sequence is 94.7% identical to SEQ ID NO:75 (1259 / 1329 = .947), and therefore it does not anticipate Claim 4 which recites "at least 95% nucleic acid sequence identity."

Claims 12 and 13 depend from Claim 6, and recites the full-length coding region of SEQ ID NO:75 or of the cDNA deposited under ATCC accession number 203247, respectively. Because the cited sequence is at best 94.7% identical to the full-length coding region of SEQ ID NO:75, the cited sequence does not anticipate Claims 12 or 13. Rejected Claims 14-16 have been canceled. Claim 17 recites a vector comprising the nucleic acid of Claim 4. The cited reference does not anticipate Claim 17 since it does not disclose a sequence which has at least 95% sequence identity to any of the recited sequences in Claim 4.

In view of the above discussion, reconsideration and withdrawal of the rejection of Claims 4, 12-13 and 17 under § 102(e) is respectfully requested.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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